SUPPORTING INFORMATION

for the communication entitled

An Approach towards the Tetracyclic Skeleton of Palhinine Alkaloids

authored by

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GENERAL EXPERIMENTAL INFORMATION.

All reactions were performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased from Aladdin, Macklin, Innochem, or TCI unless otherwise noted. Chromatographic separations were performed using Silica Gel, AR, 200-300 mesh. $^1$H and $^{13}$C NMR spectra were obtained on Varian VI-400, VI-500 and VI-600 spectrometers using CDCl$_3$ as the solvent. Infrared spectra were obtained on Thermo Scientific Nicolet iS 50. TLC analysis was visualized using UV, $p$-anisaldehyde and phosphomolybdic acid stains. High-resolution mass spectra were obtained using AB SCIEX X500R QTOF. All spectral data obtained for new compounds are reported here.

EXPERIMENTAL PROCEDURES AND COMPOUND CHARACTERIZATION

Synthesis of S1.$^1$

To a solution of cyclohexane-1,3-dione 10 (22.4 g, 200 mmol, 1.0 equiv) in benzene (123 mL) was added 2-methylpropan-1-ol (55 mL, 600 mmol, 3.0 equiv) and TsOH·H$_2$O (190 mg, 1.0 mmol, 0.005 equiv) at rt. The reaction mixture was heated with a Dean–Stark trap at 90 °C for 12 h. The solution was then concentrated under reduced pressure. The residue was purified using flash column chromatography (eluent: petroleum ether (PE)/EtOAc, ratio = 5:1) to give a yellow oil (30.9 g, 184 mmol, 92%) as the product S1.

S1: $R_f = 0.27$ (eluent: PE/EtOAc, ratio = 5:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.19 (s, 1H), 3.46 (d, $J = 6.5$ Hz, 2H), 2.28 (t, $J = 6.3$ Hz, 2H), 2.19 (t, $J = 6.7$ Hz, 2H), 1.95 –
1.80 (m, 3H), 0.90 – 0.79 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 199.5, 177.9, 102.6, 74.5, 36.7, 28.9, 27.6, 21.1, 19.0; IR (KBr) cm$^{-1}$ 3455m, 2962s, 1650m, 1610s, 1373m, 1218s, 1002m; HRMS: C$_{10}$H$_{17}$O$_2$ for [M+H]$^+$, calculated 169.1223, found 169.1222.

**Synthesis of S2.**

To a solution of $i$-Pr$_2$NH (3.7 mL, 26.5 mmol, 1.1 equiv) in THF (100 mL) was added n-BuLi (15 mL, 1.6 M in hexanes, 24.0 mmol, 1.0 equiv) slowly at –78 °C. The reaction mixture was stirred at –78 °C for 45 min. Then compound S1 (4.03 g, 24.0 mmol, 1.0 equiv) in THF (20 mL) was added slowly to the mixture at –78 °C. The mixture was left stirring at –78 °C for 45 min. Then to the solution was added 1-bromo-2-propyne (4.28 g, 36 mmol, 1.5 equiv) at –78 °C. The reaction was stirred at –78 °C for 2 h and then allowed to warm to rt. After 6 h, the reaction was quenched with sat aq NH$_4$Cl and extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd MgSO$_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 20:1) to give a yellow oil (3.76 g, 18.2 mmol, 76%) as the product S2.

**S2:** $R_f$ = 0.52 (eluent: PE/EtOAc, ratio = 10:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.18 (d, $J = 1.3$ Hz, 1H), 3.51 – 3.38 (m, 2H), 2.62 (dt, $J = 16.1$, 3.0 Hz, 1H), 2.43 – 2.27 (m, 2H), 2.26 – 2.08 (m, 3H), 1.96 – 1.80 (m, 2H), 1.76 – 1.61 (m, 1H), 0.83 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 198.2, 177.4, 102.0, 82.3, 74.7, 69.7, 44.1, 28.5, 27.6, 26.1, 19.03, 18.97, 18.95; IR (KBr) cm$^{-1}$ 3286m, 2953s, 2869w, 1666m, 1604s, 1373s, 1203s, 547s; HRMS: C$_{13}$H$_{19}$O$_2$ for [M+H]$^+$, calculated 207.1380, found 207.1377.
Synthesis of 5.

To a solution of compound S2 (4.13 g, 20 mmol, 1.0 equiv) in THF (100 mL) was added CH$_3$Li (37.5 mL, 1.6 M in ethyl ether, 60 mmol, 3.0 equiv) slowly at 0 °C. After stirred at rt for 1 h the mixture was treated with 1 M HCl (60 mL) at 0 °C. The reaction was stirred at rt for 30 min and then extracted with ethyl acetate (three times). The combined organic layers were washed with equal volume of sat aq NaHCO$_3$ and sat aq NaCl, then dried over anhyd MgSO$_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 20:1) to give a yellow oil (1.87 g, 12.6 mmol, 63%) as the product 5.

5: $R_f = 0.30$ (eluent: PE/EtOAc, ratio = 5:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.83 (s, 1H), 2.49 – 2.38 (m, 4H), 2.31 – 2.23 (m, 1H), 2.10 – 2.05 (m, 2H), 2.02 – 1.97 (m, 1H), 1.95 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 198.9, 162.7, 127.9, 81.4, 70.7, 38.5, 34.6, 27.2, 22.6, 21.4; IR (KBr) cm$^{-1}$ 3887m, 3810s, 2190m, 1666s, 1434w, 547m; HRMS: C$_{10}$H$_{13}$O for [M+H]$^+$, calculated 149.0961, found 149.0962.

Synthesis of 6

To a solution of compound 5 (37.0 mg, 0.25 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (2.5 mL) was added Et$_3$N (88.6 mg, 0.875 mmol, 3.5 equiv) and TIPSOTf (115 mg, 0.375 mmol, 1.5 equiv) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and then quenched with sat aq NaHCO$_3$. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd MgSO$_4$. After filtration and concentration, the crude dienol
silane was flushed through a short column (Et₃N-neutralized silica gel, eluent: PE) and used directly in the next step.

**Synthesis of 7**

To a solution of ZnBr₂ (11.3 mg, 0.05 mmol, 0.2 equiv) in anhydrous acetonitrile (1.0 mL) was added freshly distilled acrolein (140 mg, 2.5 mmol, 10 equiv) at 0 °C. After 15 min, to the above mixture was added a solution of compound 6 (0.25 mmol, 1.0 equiv) in anhydrous acetonitrile (1.0 mL) at 0 °C. The reaction was stirred at rt for 6 h and then heated to 60 °C for 12 h. The reaction mixture was then diluted with ethyl acetate and washed with equal volume of sat aq NaCl. The organic layer was dried over anhyd MgSO₄. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 15:1) to give a colorless oil (38.8 mg, 0.19 mmol, dr = 2:1, 76% total yield for two steps) as the product 7. The ratio of 7a and 7b was determined by ¹H NMR.

7 (diastereomeric mixture): R_f = 0.34 (eluent: PE/EtOAc, ratio = 5:1), R_f = 0.31 (eluent: PE/EtOAc, ratio = 5:1); ¹H NMR (400 MHz, CDCl₃) δ 9.81 (d, J = 2.6 Hz, 2H), 9.60 (d, J = 3.8 Hz, 1H), 5.23 (d, J = 9.0 Hz, 3H), 4.96 (d, J = 11.1 Hz, 3H), 2.89 (s, 1H), 2.76 – 2.58 (m, 8H), 2.28 – 2.09 (m, 8H), 2.04 – 1.87 (m, 8H), 1.84 – 1.77 (m, 2H), 1.42 – 1.32 (m, 3H), 1.07 (s, 6H), 0.96 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 212.3, 211.8, 202.7, 202.3, 145.3, 144.2, 112.5, 112.4, 66.1, 63.1, 49.4, 48.7, 46.0, 45.6, 41.1, 40.8, 40.1, 39.3, 38.0, 36.6, 32.0, 31.6, 26.8, 26.7, 21.4, 20.8; IR (KBr) cm⁻¹ 3424s, 2925s, 2869w, 2530m, 1725s, 1450m, 1218m, 894w, 524m; HRMS: C₁₃H₁₇O₂ for [M+H]⁺, calculated 205.1223, found 205.1220.

Further purification using column chromatography could give pure 7a.

7a: ¹H NMR (400 MHz, CDCl₃) δ 9.82 (d, J = 2.6 Hz, 1H), 5.28 (s, 1H), 5.00 (s, 1H), 2.76 (s, 1H), 2.69 – 2.59 (m, 2H), 2.32 – 2.28 (m, 1H), 2.25 – 2.19 (m, 1H), 2.16 –
2.11 (m, 1H), 2.02 – 1.91 (m, 2H), 1.86 – 1.79 (m, 1H), 1.38 – 1.32 (m, 1H), 1.07 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 212.8, 202.8, 144.0, 113.0, 66.3, 49.7, 46.2, 41.2, 39.4, 36.73, 31.7, 27.0, 21.6; IR (KBr) cm⁻¹ 3424s, 2925s, 2869w, 1725s, 1450m, 1218m, 1187w, 971w, 894w, 524m; HRMS: C₁₃H₁₇O₂ for [M+H]⁺, calculated 205.1223, found 205.1220.

**Synthesis of 8**

To a solution of ZnBr₂ (11.3 mg, 0.05 mmol, 0.2 equiv) in anhydrous acetonitrile (1.0 mL) was added N-phenylmaleimide (432 mg, 2.5 mmol, 10 equiv) at 0 °C. After 15 min, to the above mixture was added a solution of compound 6 (0.25 mmol, 1.0 equiv) in anhydrous acetonitrile (1.0 mL) at 0 °C. The reaction mixture was stirred at rt for 6 h and then heated at 70 °C for 12 h. The reaction mixture was then diluted with ethyl acetate and washed with equal volume of sat aq NaCl. The organic layer was dried over anhyd MgSO₄. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 5:1) to give a white solid (51.4 mg, 0.16 mmol, 64% in two steps from compound 5) as the product 8.

8: R₉ = 0.32 (eluent: PE/EtOAc, ratio = 2:1); mp 242 – 244 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.45 (t, J = 7.3 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 5.34 (s, 1H), 5.09 (s, 1H), 3.23 (dd, J = 9.5, 3.5 Hz, 1H), 3.07 (d, J = 9.5 Hz, 1H), 2.89 – 2.80 (m, 3H), 2.27 – 2.21 (m, 1H), 2.19 – 2.10 (m, 1H), 2.06 (d, J = 16.8 Hz, 1H), 1.59 (dd, J = 13.8, 4.1 Hz, 1H), 1.38 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 209.0, 175.9, 175.3, 143.8, 131.5, 129.2, 128.9, 126.6, 113.9, 63.8, 46.3, 45.8, 43.4, 43.2, 39.4, 31.5, 20.4; IR (KBr) cm⁻¹ 3471m, 2314m, 1712s, 1496w, 1388s, 1203s, 694m; HRMS: C₂₀H₂₀NO₃ for [M+H]⁺, calculated 322.1438, found 322.1436;

**Synthesis of 9**


To a solution of ZnBr$_2$ (11.3 mg, 0.05 mmol, 0.2 equiv) in anhydrous acetonitrile (1.0 mL) was added nitroethene (182 mg, 2.5 mmol, 10 equiv) at rt. After 15 min, to the above mixture was added a solution of compound 6 (0.25 mmol, 1.0 equiv) in anhydrous acetonitrile (1.0 mL) at rt. The reaction mixture was heated at 90 °C for 12 h (using a sealed tube). The reaction mixture was then diluted with ethyl acetate and washed with equal volume of sat aq NaCl. The organic layer was dried over anhyd MgSO$_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 15:1) to give a yellow solid (21.9 mg, 0.10 mmol, 40% in two steps from compound 5) as the product 9.

9: $R_f = 0.31$ (eluent: PE/EtOAc, ratio = 5:1); mp 89 – 92 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.33 (s, 1H), 5.02 (s, 1H), 4.88 (dd, $J = 10.1, 5.2$ Hz, 1H), 3.10 (s, 1H), 2.77 – 2.68 (m, 1H), 2.41 (m, 2H), 2.32 – 2.25 (m, 1H), 2.17 – 2.11 (m, 1H), 2.04 – 1.94 (m, 2H), 1.48 – 1.40 (m, 1H), 0.95 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 209.9, 144.0, 113.4, 86.1, 62.2, 47.6, 40.5, 38.6, 38.5, 33.1, 31.5, 19.1; IR (KBr) cm$^{-1}$ 3409m, 2962s, 1712s, 1550s, 1373s, 894s, 678s, 524s; HRMS: C$_{12}$H$_{16}$NO$_3$ for [M+H]$^+$, calculated 222.1125, found 222.1121;

**Synthesis of 11.$^4$**

To a solution of cyclohexane-1,3-dione 10 (67.3 g, 600 mmol, 1.0 equiv) in a mixed solvent of N,N-diisopropylethylamine (90 mL) and water (90 mL) was added 1,3-dibromopropane (30.6 mL, 300 mmol, 0.5 equiv) slowly at rt. The reaction mixture was heated at 90 °C for 3.5 h and then treated with 2 M HCl (150 mL) slowly at rt. After 15 min, the reaction was extracted four times with ethyl acetate. The combined
organic layers were washed with equal volume of sat aq NaHCO$_3$ and sat aq NaCl, then dried over anhyd MgSO$_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 2:1) to give a colorless oil (20.5 g, 135 mmol, 45%) as the product 11.

11: $R_f = 0.20$ (eluent: PE/EtOAc, ratio = 4:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.03 (t, $J = 5.1$ Hz, 2H), 2.29 (m, 4H), 2.16 (t, $J = 6.3$ Hz, 2H), 1.92 – 1.84 (m, 2H), 1.83 – 1.76 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 198.1, 171.5, 111.6, 67.3, 36.6, 28.6, 21.4, 20.8, 17.5; IR (KBr) cm$^{-1}$ 3517w, 2946m, 2360m, 1650s, 1619s, 1403s, 863m; HRMS: C$_9$H$_{13}$O$_2$ for [M+H]$^+$, calculated 153.0910, found 153.0907.

**Synthesis of 12**

![Chemical structure](image)

To a solution of i-Pr$_2$NH (7.4 mL, 53 mmol, 1.1 equiv) in THF (200 mL) was added n-BuLi (31.9 mL, 1.6 M in hexanes, 51 mmol, 1.06 equiv) slowly at –78 °C. The reaction mixture was stirred at –78 °C for 45 min. Then compound 11 (7.30 g, 48 mmol, 1.0 equiv) in THF (20 mL) was added slowly to the mixture at –78 °C. The mixture was left stirring at –78 °C for 1.5 h. Then to the reaction was added a solution of 3-trimethylsilyl-1-bromo-2-propyne (13.76 g, 72 mmol, 1.5 equiv) in THF (20 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 3 h and then allowed to warm to rt. After 6 h, the reaction was quenched with sat aq NH$_4$Cl and extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd MgSO$_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 10:1) to give a white solid (10.50 g, 40 mmol, 83%) as the product 12.

12: $R_f = 0.36$ (eluent: PE/EtOAc, ratio = 8:1); mp 71 – 75 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.20 – 4.07 (m, 1H), 4.05 – 3.92 (m, 1H), 2.88 (dd, $J = 17.0$, 3.6 Hz, 1H),
2.51 – 2.07 (m, 7H), 1.89 – 1.63 (m, 3H), 0.11 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 197.2, 170.9, 110.8, 105.4, 85.8, 67.2, 43.9, 27.8, 25.6, 21.3, 20.8, 17.5, 0.00; IR (KBr) cm$^{-1}$ 2962m, 2175s, 1866m, 1619s, 833s; HRMS: C$_{15}$H$_{23}$O$_2$Si for [M+H]$^+$, calculated 263.1462, found 263.1455;

**Synthesis of S4:**

![Synthesis Diagram]

To a solution of 3-bromopropan-1-ol S3 (10.0 g, 72 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (180 mL) was added imidazole (7.82 g, 115 mmol, 1.6 equiv) at rt. After 15 min, TBSCl (12.9 g, 86 mmol, 1.2 equiv) was added to the mixture at 0°C. The reaction mixture was stirred at rt for 18 h and then quenched with sat aq NaHCO$_3$. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd MgSO$_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE) to give a colorless oil (16.7 g, 66 mmol, 92%) as the product S4.

**S4:** $R_f$ = 0.48 (eluent: PE); $^1$H NMR (400 MHz, CDCl$_3$) δ 3.72 (t, $J$ = 5.7 Hz, 2H), 3.50 (t, $J$ = 6.5 Hz, 2H), 2.07 – 1.97 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 60.4, 35.6, 30.5, 25.9, 18.3, -5.4; IR (KBr) cm$^{-1}$ 3394s, 2931s, 2854m, 1249s, 1101s, 833s, 771s; HRMS could not be obtained.

**Synthesis of S5**

![Synthesis Diagram]

To a mixture of magnesium turnings (4.32 g, 180 mmol, 3 equiv) in THF (46 mL) was added 1,2-dibromoethane (1.13 g, 6 mmol, 0.1 equiv) slowly at rt. The reaction mixture was stirred at rt for 20 min. Then compound S4 (0.25 mmol, 1.0 equiv) in THF (46 mL) was added slowly to the mixture at 50°C. After stirring at 50°C for 15
min, THF was added slowly to the solution until the precipitate was completely dissolved at rt. The solution of S5 was used directly in the next step.

**Synthesis of 13**

![Chemical Structure](image)

To a solution of 12 (4.49 g, 17.1 mmol, 1.0 equiv) in THF (17 mL) was added Grignard reagent S5 (120 mL, 60 mmol, 3.5 equiv) slowly at −10 °C. The reaction mixture was stirred at rt for 4 h and then treated with 1.5% H₂SO₄ (26 mL) slowly at 0 °C. After the reaction was stirred at rt for another 10 min, the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaHCO₃ and sat aq NaCl, then dried over anhyd MgSO₄. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 4:1) to give a yellow oil (4.78g, 10.9 mmol, 64%) as the product 13.

**13:** \( R_f = 0.19 \) (eluent: PE/EtOAc, ratio = 4:1); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 3.56 (t, \( J = 5.8 \) Hz, 2H), 3.48 – 3.25 (m, 2H), 3.12 (s, 1H), 2.60 – 2.19 (m, 8H), 2.19 – 1.90 (m, 3H), 1.71 – 1.33 (m, 4H), 0.81 (s, 9H), 0.03 (s, 9H), -0.03 (s, 6H); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 199.7, 161.7, 135.8, 104.5, 87.0, 62.4, 61.1, 37.5, 33.8, 32.4, 31.6, 29.0, 26.6, 25.9, 23.2, 20.8, 18.2, 0.0, -5.3; IR (KBr) cm\(^{-1}\) 3363m, 2951s, 2175s, 1650s, 1249s, 1187m, 1095s, 845s, 771s; HRMS: C₂₄H₄₅O₃Si₂ for [M+H]\(^+\), calculated 437.2902, found 437.2894.
Synthesis of 14

To a solution of 13 (1.44 g, 3.3 mmol, 1.0 equiv) in THF (35 mL) was added 2-nitrobenzenesulfonamide (2.00 g, 9.9 mmol, 3.0 equiv) and PPh$_3$ (1.21 g, 4.6 mmol, 1.4 equiv) at rt. After 10 min, DIAD (0.87 g, 4.3 mmol, 1.3 equiv) was added to the above mixture at rt. The reaction mixture was heated at 70 °C for 12 h before being concentrated under reduced pressure. The crude sulfonamide was flushed through a short column (silica gel, eluent: PE/EtOAc, ratio = 5:1) and then used directly in the next step.

To a solution of the crude sulfonamide in THF (35 mL) was added TBAF (1.0 M in THF; 13 mL, 13 mmol, 3.9 equiv) slowly at rt. The reaction mixture was stirred for 12 h at rt before being quenched with sat aq NH$_4$Cl. Then the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd MgSO$_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 1:1) to give a yellow oil (1.06 g, 2.4 mmol, 74%) as the product 14.

14: $R_f$ = 0.14 (eluent: PE/EtOAc, ratio = 1:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.11 – 8.00 (m, 1H), 7.82 – 7.74 (m, 1H), 7.74 – 7.65 (m, 2H), 6.05 – 5.89 (m, 1H), 3.64 (t, $J$ = 5.9 Hz, 2H), 3.17 – 2.85 (m, 2H), 2.82 – 1.83 (m, 13H), 1.79 – 1.69 (m, 1H), 1.69 – 1.40 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 199.0, 161.2, 148.0, 135.4, 133.7, 133.6, 132.8, 130.9, 125.2, 82.0, 70.7, 62.0, 43.4, 37.3, 33.6, 31.3, 29.3, 29.0, 26.3, 22.1, 21.7; IR (KBr) cm$^{-1}$ 3293m, 2931s, 2329m, 1655s, 1543s, 1342s, 1172s, 848m, 740s; HRMS: C$_{21}$H$_{27}$N$_2$O$_6$S for [M+H]$^+$, calculated 435.1584, found 435.1580.
Synthesis of 15

To a solution of compound 14 (1.30 g, 3 mmol, 1.0 equiv) in toluene (200 mL) was added PPh$_3$ (2.44 g, 9.3 mmol, 3.1 equiv) at rt. After 10 min, a solution of DEAD (1.57 g, 9 mmol, 3.0 equiv) in toluene (4 mL) was added slowly to the above mixture at rt. The reaction was stirred at rt for 1 h before being concentrated under reduced pressure. The crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 1:1) to give the crude 15. To a mixture of the crude 15 in EtOH (30 mL) was added ZnCl$_2$ (0.82 g, 6 mmol) at rt. The reaction mixture was stirred at rt for 18 h before being filtered and concentrated. The crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 2:1) to give a white solid (0.86 g, 2.1 mmol, 70%) as the product 15.

**15**: $R_f = 0.23$ (eluent: PE/EtOAc, ratio = 2:1); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.90 (dd, $J = 7.7$, 1.4 Hz, 1H), 7.68 (m, 2H), 7.57 (dd, $J = 7.7$, 1.3 Hz, 1H), 3.52 (dt, $J = 15.0$, 4.9 Hz, 1H), 3.38 (dt, $J = 15.0$, 5.1 Hz, 1H), 3.04 (td, $J = 13.2$, 4.2 Hz, 1H), 2.91 (ddd, $J = 14.6$, 9.8, 4.5 Hz, 1H), 2.82 (ddd, $J = 14.6$, 9.6, 4.6 Hz, 1H), 2.71 (dt, $J = 13.7$, 4.7 Hz, 1H), 2.64 – 2.52 (m, 3H), 2.51 – 2.45 (m, 1H), 2.43 – 2.31 (m, 3H), 2.27 – 2.16 (m, 2H), 2.11 – 1.99 (m, 3H), 1.92 – 1.81 (m, 1H), 1.82 – 1.73 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 197.9, 159.2, 148.8, 136.2, 133.8, 131.4, 130.7, 130.6, 124.0, 82.0, 70.6, 53.7, 53.3, 36.5, 33.7, 28.0, 27.4, 27.3, 26.1, 21.8, 21.5; IR (KBr) cm$^{-1}$ 3452s, 1650s, 1357m, 848w, 740w, 571s; HRMS: C$_{21}$H$_{25}$N$_2$O$_5$S for [M+H]$^+$, calculated 417.1479, found 417.1476; m.p. = 139-141 °C.
Synthesis of 16 (optimized procedure)

To a solution of 15 (33.3 mg, 0.08 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (0.8 mL) was added Et$_3$N (28.3 mg, 0.28 mmol, 3.5 equiv) and TIPSOTf (36.7 mg, 0.12 mmol, 1.5 equiv) at –78 °C. The reaction mixture was stirred at –78 °C for 1.5 h before being quenched with sat aq NaHCO$_3$. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd MgSO$_4$. After filtration and concentration, the crude dienol silane 1 was flushed through a short column (Et$_3$N-neutralized silica gel, eluent: PE/EtOAc, ratio = 5:1) and then used directly in the next step.

To a solution of ZnBr$_2$ (3.6 mg, 0.016 mmol, 0.2 equiv) in anhydrous acetonitrile (0.4 mL) was added freshly distilled acrolein (44.8 mg, 0.8 mmol, 10 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. After that, the reaction mixture was treated with a solution of crude 1 (prepared from 0.08 mmol 15, 1.0 equiv) in 0.4 mL mixed MeCN/CH$_2$Cl$_2$ (1.5:1) at 0 °C. The reaction mixture was stirred at rt for 18 h and then diluted with ethyl acetate. The organic layer was washed with equal volume of sat aq NaCl and dried over anhyd MgSO$_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 4:1) to give a white solid (24.8 mg, 0.053 mmol, 66% in two steps from compound 15) as the product 16, a white solid (5.1 mg, 0.012 mmol, 15% in two steps from compound 15) as the product 17 and a white solid (4.1 mg, 0.010 mmol, 12%) as the compound 15. The reaction could be scale up to a 1.2 g scale using the same procedure.

**16**: $R_f = 0.24$ (eluent: PE/EtOAc, ratio = 2:1), mp 168 – 171 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.89 (d, $J = 1.9$ Hz, 1H), 7.93 – 7.87 (m, 1H), 7.72 – 7.62 (m, 2H), 7.62 –
7.55 (m, 1H), 5.25 (dd, $J = 2.4$, 1.4 Hz, 1H), 5.05 (d, $J = 1.3$ Hz, 1H), 3.43 – 3.29 (m, 2H), 3.27 – 3.06 (m, 3H), 2.77 – 2.59 (m, 2H), 2.45 – 2.32 (m, 1H), 2.28 – 2.20 (m, 2H), 2.03 – 1.80 (m, 9H), 1.76 – 1.67 (m, 1H), 1.36 (dt, $J = 13.8$, 3.2 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 213.5, 202.5, 148.4, 146.5, 133.6, 132.0, 131.6, 130.5, 124.1, 114.6, 68.2, 50.7, 50.0, 49.3, 44.2, 41.5, 39.7, 39.7, 31.0, 30.4, 26.5, 25.1, 23.3; IR (KBr) cm$^{-1}$ 3101m, 2962s, 1726s, 1527s, 1157s, 848m, 740s, 571s; HRMS: C$_{24}$H$_{29}$N$_2$O$_6$S for [M+H]$^+$, calculated 473.1741, found 473.1744;

17: $R_f = 0.26$ (eluent: PE/EtOAc, ratio = 2:1); mp 176 – 178 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.92 (dd, $J = 7.6$, 1.7 Hz, 1H), 7.75 – 7.64 (m, 2H), 7.57 (dd, $J = 7.5$, 1.6 Hz, 1H), 5.27 (s, 1H), 5.01 (s, 1H), 3.42 (d, $J = 4.2$ Hz, 1H), 3.40 – 3.31 (m, 1H), 3.26 – 3.16 (m, 1H), 3.08 – 2.83 (m, 4H), 2.66 – 2.50 (m, 3H), 2.46 – 2.37 (m, 1H), 2.27 – 2.14 (m, 2H), 2.10 – 1.96 (m, 3H), 1.89 – 1.78 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 197.9, 163.5, 148.9, 145.9, 133.8, 131.9, 131.3, 130.7, 130.4, 124.0, 111.2, 58.1, 54.3, 54.0, 40.9, 39.8, 36.2, 29.3, 27.6, 27.0, 21.1; IR (KBr) cm$^{-1}$ 2926m, 1664s, 1538s, 1355m, 1165s, 892m, 742m, 577s; HRMS: C$_{21}$H$_{25}$N$_2$O$_5$S for [M+H]$^+$, calculated 417.1479, found 417.1474;
CRYSTALLOGRAPHIC DATA OF 9 (CCDC 1974776)

Supplementary Figure 1 X-ray structure of 9.

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2Θ range for data collection 6.6 to 52°

Index ranges -9 ≤ h ≤ 9, -14 ≤ k ≤ 14, -15 ≤ l ≤ 15

Reflections collected 14444

Independent reflections 4254[ R (int) = 0.0331 (inf-0.9Å)]

Data/restraints/parameters 4254/0/291

Goodness-of-fit on F² 1.031

Final R indexes [I>2σ (I) i.e. F_o>4σR_I = 0.0409, wR² = 0.0940 (F_o)]

Final R indexes [all data] R_I = 0.0520, wR² = 0.1009

Largest diff. peak/hole / e Å⁻³ 0.258/-0.233

Flack Parameters N

Completeness 0.9982
CRYSTALLOGRAPHIC DATA OF 16 (CCDC 1905335)

Supplementary Figure 2 X-ray structure of 16.

Identification code 190322c
Empirical formula C_{24}H_{28}N_{2}O_{6}S
Formula weight 472.54
Temperature / K 298 (2) K
Crystal system Monoclinic
Space group P2 (1)/c
Unit cell dimensions a = 8.7885 (9) Å
b = 8.7617 (9) Å
c = 28.539 (3)Å
α/°, β/°, γ/° 90 °, 94.8440 (10)°, 90°
Volume 2189.7 (4) Å³
Z 4
Density (calculated) 1.433 mg mm⁻³
μ / mm⁻¹ 0.194
F(000)  1000
Crystal size  0.45 × 0.32 × 0.27 mm³
2Θ range for data collection  2.43 to 25.02°
Index ranges  -8 ≤ h ≤ 10, -9 ≤ k ≤ 10, -24 ≤ l ≤ 33
Reflections collected  10584
Independent reflections  3868 [ R (int) = 0.0370]
Data/restraints/parameters  3868 / 0 / 298
Goodness-of-fit on F²  1.031
Final R indexes [I>2σ (I) i.e. F_o>4σ (F_o)] R₁ = 0.0489, wR₂ = 0.1071
Final R indexes [all data] R₁ = 0.0781, wR₂ = 0.1186
Largest diff. peak/hole / e Å⁻³  0.238 / -0.304
Completeness  0.998
Supplementary Table 1. Model Study using other dienophiles

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<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>=CH=CH</td>
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<sup>a</sup>Reactions are carried out with 0.2 mmol 6, 2 mmol dienophile, 0.04 mmol ZnBr<sub>2</sub> in 1.6mL MeCN.
Supplementary Table 2. Optimization of the key reaction

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<td>53  21 24</td>
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</table>
All reactions were carried out using crude dienol silane 1 (prepared from 0.08 mmol 15), 0.8 mmol acrolein and 0.016 mmol Lewis acid with the indicated solvent and reaction temperature. *Amount of the added Lewis acid. †Isolated yield for two steps. ‡1.2 g scale reaction.

REFERENCES


